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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/727,576
Filing Date: December 05, 2003
Appellant(s): SHARMA ET AL.

Tu A. Phan
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 3/1/2011 appealing from the Office action mailed 1/12/2010.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 18-35 are pending and rejected.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner.

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

6,190,857 Ralph et al. 2-2001

Lucas, J. Identification and Characterization of Genes Differentially Expressed in Breast Ductal Carcinoma in situ, Journal of Investigative Medicine, Vol. 45, no. 1 (1997) , p. 132A.

Wadhwa, R. et al. An Effective Elimination of False Positives Isolated from Differential Display of mRNAs, Molecular Biotechnology, Vol. 6 (1996), pp. 213-217.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

1. Claims 18 and 20-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ralph et al. (US 6,190,857; as cited in IDS) in view of Lukas (Journal of Investigative Medicine, 1997, Vol. 45, No. 1, page 132A).

Ralph et al. teach a method for cancer detection and diagnosis that relies upon detecting a response of circulating leukocytes to the disease state (Col. 4, line 66-Col. 5, line 14). Ralph et al. teach that the method described in their disclosure may be used to discover disease markers for any disease state that affects the peripheral blood leukocytes, including but not limited to organ defined cancer (Col. 10, lines 2-3). To that end, Ralph et al. teach a method which includes steps of providing human peripheral blood mRNAs from both healthy and diseased individuals, amplifying the mRNAs to provide nucleic acid amplification products, separating the nucleic acid amplification products, and selecting those mRNAs that are differentially

expressed between normal individuals and individuals having a disease state (Col. 9, lines 35-43). Ralph et al. further teach a variety of further methods in which the identified markers could be used- to identify and isolate full length gene sequences, cDNA sequences, or to select segments for use in detection, diagnostic or prognostic methods, vector constructs and the like (Col. 16 and throughout). The practice of any of these methods would first require that the differentially expressed markers had been isolated, as required in instant claim 18. Further, when Ralph et al. exemplify their method for the identification of markers of metastatic prostate cancer, they teach "cutting differentially appearing bands out of the gel" and subsequent cloning and sequencing of the bands (Col. 62, lines 60-65).

The differential display method exemplified by Ralph et al. employs gel electrophoresis as the means to separate the amplification products, and this is a non-sequence based technique (Col. 62, and throughout).

Ralph et al. teach that their method may also comprise the step of converting RNAs into cDNAs using reverse transcriptase (Col. 9 line 45 and following), and they exemplify this step in the methods throughout the document.

Ralph et al. do not teach this method wherein the organ defined cancer is very early stage breast cancer. Ralph et al. do not exemplify a method wherein at least ten differently expressed markers are isolated, nor do they exemplify a method wherein between 50 and 100 are selected or between 10 and 500.

Lukas undertakes differential display analysis in order to identify genes which are differentially expressed in breast ductal carcinoma in situ (DCIS) relative to invasive breast carcinoma, and identified 119 mRNA species which were differentially expressed. Lukas

teaches that the identification and characterization of genes involved in early breast carcinogenesis may further our understanding of the molecular pathogenesis of cancer in general and may also lead to identification of breast-cancer specific molecular markers with potential predictive value.

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Ralph et al. so as to have applied them to the study and diagnosis of DCIS, following the guidance of Lukas. One would have been motivated by the teachings of Ralph et al. that their methods can be applied to any organ defined cancer (which DCIS is) and by the teachings of Lukas of the desirably to identify genes involved in early breast carcinogenesis. Furthermore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have isolated as many differentially expressed markers as possible, including 10, 20, 100, 500, provided that the markers existed in the two sample types. At the time the invention was made, it was widely known that performing differential display methods with different beginning primer sets would result in the isolation of non-redundant sequences, and it was routine to practice the method with a variety of primer sets in order to provide one of skill in the art with the means to gather as many differently expressed markers as possible.

Thus, following the teachings of Ralph et al. in view of Lukas, the claimed invention is prima facie obvious.

2. Claims 19, 26, 27, 28, 29, 30, 31, 32, 33, 34, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ralph et al. in view of Lukas as applied to claims above, and further in view of Wadhwa et al. (Molecular Biotechnology, Volume 6, pages 213-217).

The teachings of Ralph et al. in view of Lukas are previously discussed.

Ralph et al. teach that an advantage of their method is that there is no need to directly sample tumor cells in order to detect cancer markers as such markers may instead be detected by sampling circulating cells of the immune system, circumventing the problem of having to first identify the location of a tumor in the body before being able to able to analyze it (Col. 5, lines 45-54). Regarding claims 27, 28, and 29, Ralph et al. teach that once such a disease state marker is identified, various detection methods are known for screening and diagnostic purposes, teaching, for example that the mRNA species themselves may be detected, for example, by Northern blotting, RT-PCR, slot-blotting, and similar methods well known in the art (Col. 6, lines 43-48). Northern blotting and slot-blotting are both methods include steps of hybridizing test mRNA or cDNA with the marker probes that are cDNA are present at a different level in cells in a blood sample from more than one normal human than in corresponding cells in a blood sample from more than one human who are known to have the disease state. Ralph et al. teach that the method of detecting human disease comprises detecting the quantity of a disease marker expressed in human peripheral blood and comparing the quantity of the marker to the quantity expressed in the blood of a normal individual, where a difference in quantity of expression is indicative of a disease state (Col. 10, lines 32-50, and throughout).

However, Ralph et al. in view of Lukas do not teach a method wherein the identified isolated nucleic acid markers are prepared on a solid support, namely a solid support which is a filter.

Wadhwa et al. teach a reverse northern assay of DNA fragments isolated from differential display, and teach that this type of method has advantages over traditional Northern blots,

including that it requires less time, and it is particularly useful as many of the isolated bands from differential display are small in size and would not serve a good probes from Northern analysis (p. 216). In this method, the isolated differentially displayed molecules were PCR amplified, bound to a membrane filter, and probed cDNA probes prepared from total RNA from cells. The isolated cDNA probes were labeled.

It would have been prima facie obvious to one of ordinary skill in the art to have substituted the Northern assays taught by Ralph et al. in view of Lukas with the reverse Northern assays taught by Wadhwa et al. Because both references teach methods for detecting nucleic acids in samples, it would have been obvious to one skilled in the art to substitute one method for the other to achieve the predictable result of detecting target nucleic acids in samples.

(10) Response to Argument

The remarks are addressed in the order they are presented.

Appellant states on page 9 that the arguments and declarations of record are commensurate in scope with all of the claimed invention since all of the claims provide a method of identifying transcripts or probes from a breast cancer sample that serve "as a set of markers for diagnosis of very early stage breast cancer." This intended use is set forth in some, but not all of the claims. Further, it remains, that not all of the claims are drawn to actually diagnosing diseases, some contain only the requisite steps to identify the markers. All merits of the declarations were addressed in either case, and even if the declarations and arguments are considered commensurate in scope with the claims, they remain unpersuasive for the reasons reiterated herein.

On pages 10-11 of the brief Appellant points out that neither Ralph et al. alone nor Lukas alone teach all of the limitations of the instantly claimed invention. This is not disputed. On page 11 Appellant states that in view of these deficiencies (and others to be discussed) neither reference alone or in combination teaches all of the claim limitations. This cursory statement is a piecemeal analysis that does not consider the totality of the rejection. The additional arguments set forth are addressed in turn.

In the heading of section (A)(2) on page 12 Appellant states first, that Ralph et al. does not teach or suggest detection of a non-metastatic or pre-metastatic very early stage breast cancer, and that Ralph makes clear that the early stage of disease would encompass a metastasizing tumor.

The examiner disagrees with these two points, which are repeated throughout the brief. Ralph et al. positively state that their method would be useful for diagnosis of breast cancer (Abstract). Ralph et al. state that their method would be applicable to metastatic and organ defined cancers (Col. 10, lines 2-3). Here, Ralph et al. clearly makes a distinction between what is viewed by the reference as two types of cancer: organ defined versus metastatic. So, this is a clear suggestion that Ralph et al. considers their method would function prior to a cancer becoming metastatic, in particular when the cancer remains organ defined. Further, Ralph et al. positively state that "it is expected that detection may be feasible at very early stages of disease progression, when there are few or no circulating cells present in the peripheral blood (Col. 5, lines 10-11; emphasis added)." Ralph specifically teaches that their method "relies upon detecting a response to the circulating leukocytes to the disease state" (Col. 5, lines 2-4). Ralph further teaches that the markers can be used to identify disease "before individuals exhibit the

disease state (such as a tumor)," and the methods are suitable for widespread screening of asymptomatic individuals (Col. 14, line 55 and following). The secondary reference is used to establish that at the time the invention was made there was a desire to identify molecular markers for very early stage breast cancer. Thus, contrary to Appellant's assertion, Ralph et al. do in fact suggest detection of non-metastatic or pre-metastatic very early stage breast cancer.

Appellant states that one of ordinary skill in the art would only have extrapolated the teachings of Ralph to other cancers that have reached a metastatic phenotype, and this does not include very early stage breast cancer, and so the examiner's extrapolation of the teachings of Ralph to detection of cancers which have not reached a metastatic phenotype constitutes impermissible hindsight. In support of this position, appellants refer to paragraphs 11, 12 and 16 of the second Mackay declaration which was filed December 1, 2009. In these sections, Dr. Mackay represents his opinion that Ralph et al. provides a method which identifies cancers which have begun to exhibit phenotypic changes that effectively provide markers of a metastatic phenotype. It is agreed that Ralph et al. only exemplify identifying markers for a metastatic phenotype. The suggestion to apply the methods of Ralph et al. to cancers that are organ defined and have few or no circulating cells from the direct statements of Ralph et al. Appellant's argument is grounded in the fact that the examples in Ralph et al. are limited only to metastatic breast and prostate cancer. The reference should not be limited only to the teachings of the working examples, but instead should be considered for all that it reasonably suggests, including nonpreferred embodiments (MPEP 2123(I)). Here, Ralph expressly states that their invention is useful for identification of markers for, and detection of, "very early stages of disease," organ

defined cancers, and breast cancer. Ralph is clearly suggestive of the application of their method to very early stage cancer and to breast cancer.

Appellant reiterates the position that Ralph does not teach or suggest detection of non-metastatic or pre-metastatic very early stage breast cancer, pointing to the first declaration by Dr. Mackay and paragraphs 6-15 of the second declaration filed by Dr. Mackay.

In the first declaration, Dr. Mackay states that he believes that the skilled person reading Ralph et al. would have understood that the method described by Ralph et al. was based on the release of cancer cells, their debris, or cellular components into the blood system resulting in direct interaction between cancer cells and the blood cells, thereby affecting gene expression of the blood cells (paragraph 5). However, this is in direct contrast to the express teachings of Ralph et al. which teaches "...since the markers are produced by circulating leukocytes rather than diseased cells, it is expected that detection may be feasible at very early stages of disease progression, when there are few of no circulating cells present in the peripheral blood (Col. 5, lines 7-11)."

In the first declaration, Dr. Mackay points to two passages from Ralph et al. to support an assertion that Ralph et al state that direct contact between the sample to be analyzed and the diseased cells is necessary. Both of these passages are in a portion of Ralph et al. that discusses Immunodetection Assays, not the identification of markers based on mRNA expression. When Ralph et al. discuss the identification of markers based on differential mRNA expression, their only qualification for the sample is that it be a tissue or fluid where leukocytes may be present (Col. 53, lines 1-5). There is no mention that it is required or even preferred that there be direct interaction between cancer cells or their debris or cellular components.

The first declaration states that "the skilled person would believe that the Ralph et al. method could only be extended to cancers in which contact between the cancer cells and peripheral blood cells occurred (paragraph 9)." The declaration suggests that this happens only once cells with metastatic potential or metastasis appear. However, this opinion is contraindicated by the express teachings of Ralph et al. and the general knowledge of the constantly circulating function of white blood cells. At the time the invention was made, one of ordinary skill in the art certainly would have known that white blood cells spend most of their time outside the circulatory system, patrolling through interstitial fluid and the lymphatic system (Campbell. 1996, page 833). So, it would have been expected that leukocytes would have come in contact with the tumor cells, even if no blood vessels had invaded the tumor. This is reflected in Ralph et al.'s express teaching that detection would be feasible even when there are few of no circulating cancer cells, as stated by Ralph et al., at very early stages of disease progression.

In paragraph 15 of the second declaration (filed 12/1/09) Dr. Mackay states that even if one were to consider attempting the claimed invention based on the teachings of Ralph he would not have expected such cancers to be detectable by altered gene expression in blood samples because the cancer cells have not reached metastatic potential and have not released their debris into the blood system. Dr. Mackay refers to the "absence of contact between the blood cells and cancer cells," their components or debris. This is not persuasive because, at the time the invention was made, it was established that blood cells spend most of their time outside the circulatory system, patrolling through interstitial fluid and the lymphatic system. Further, as noted, Dr. Mackay's statements remain in direct contrast to the express teachings of Ralph et al. which teaches "…since the markers are produced by circulating leukocytes rather than diseased

cells, it is expected that detection may be feasible at very early stages of disease progression, when there are few of no circulating cells present in the peripheral blood."

On page 13 of the brief, Appellant states that the examiner states that there is no requirement for "direct interaction between cancer cells, their debris, or cellular components." The examiner does not make such a statement. To the contrary, the examiner has argued that even before a tumor is metastatic, it was known at the time of filing that leukocytes would have come in contact with the tumor since white blood cells spend most of their time outside the circulatory system, patrolling through interstitial fluid and the lymphatic system.

Appellant argues that the mere contact between a blood cell and a tumor cell is not enough to allow detection by Ralph. There is no experimental evidence on the record to support this assertion. There is no distinction between the actual process steps suggested by Ralph et al. and those practiced in the instant claims, and so, if one were expected to work so would the other. Appellant points to paragraphs 19-21 of the second Mackay declaration in support of this position. The declaration states that the success of the method taught by Ralph is based on "the requirement for the cancer cell to have reached metastatic potential and thus, to display a metastatic phenotype." Ralph never makes this requirement, Appellant has imputed in onto the disclosure of Ralph. In the declaration Dr. Mackay points out that Ralph makes no mention that blood cells that are sampled in the peripheral blood have been altered in terms of their gene expression by contact with tumor cells at the tumor site (paragraph 19). Ralph is not required to disclose the precise mode of action of the gene expression modification. Nonetheless, Ralph does state that their invention is based on detecting a response of circulating blood cells "to the disease state" in conjunction with their statement that there need not be circulating diseased cells

present in the peripheral blood. Thus, it appears that Ralph is clearly suggestive that the effect on the blood cells does not necessarily occur due to contact from circulating debris, as Appellant asserts. Ralph makes no such requirement, even though Appellant and Dr. Mackay repeatedly argue that they do.

Dr. Mackay points to two passages from Ralph et al. to support an assertion that Ralph et al. state that direct contact between the sample to be analyzed and the diseased cells is necessary. Both of these passages are in a portion of Ralph et al. that discusses Immunodetection Assays, not the identification of markers based on mRNA expression. When Ralph et al. discuss the identification of markers based on differential mRNA expression, their only qualification for the sample is that it be a tissue or fluid where leukocytes may be present (Col. 53, lines 1-5). There is no mention that it is required or even preferred that there be direct interaction between cancer cells or their debris or cellular components.

In paragraph 21 of the declaration, Dr. Mackay asserts that "the mere contact of blood cell with a tumor cell is not enough." Suggesting that this would not be sufficient to lead to changes in gene expression in blood samples. However, there is no evidence on the record to support this opinion statement.

Appellant sets forth that even if blood cells did come into contact with very early stage breast cancer no response of the kind observed by Ralph would have been expected. Absolute expectation of success is not a requirement to establish obviousness of an invention. Here, there was a recognized problem in the art- as supported by Lukas- namely to identify markers for the detection of very early stage breast cancer, and the use of those markers to detect the condition. Ralph provide clear teaching of a method for screening for markers in blood samples, it is

undisputed on this record that the molecular biology techniques used by Ralph were routinely employed at the time the invention was made. The contribution provided by Ralph was to look to the blood for the detection of markers of disease at very early stages of disease, diseases which Ralph clearly discloses as including organ defined cancers and breast cancer. One of ordinary skill in the art could have employed the methods of finding the markers in patients having very early stage breast cancer, and, if the markers were present, would have had an excellent chance of success in identifying using the methodologies exemplified by Ralph or other routinely used methods for assay of expression levels of genes in the blood. As noted in the Supreme Court decision KSR, "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely that product [was] not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103." KSR 82 USPQ2d at 1397.

Appellant argues, and Dr. Mackay asserts that there is nothing in Ralph that would have guided one of ordinary skill in the art to make the leap to detection of cancers which are phenotypically different and which have not reached metastatic potential (brief page 14 or response, and paragraph 22 of the second declaration). However, Ralph et al. expressly suggest that their method is relevant to "very early stage" disease (the same language used in the instant claims) and they specifically identify breast cancer as a disease (throughout), and they specifically state that the invention is relevant to metastatic OR organ defined cancers (Col. 10, lines 2-3). Ralph is explicit in providing that their invention is relative to either alternative. Appellant points out that Ralph et al. state that it may be possible to use its method at "very early

stages of disease progression." Appellant states that Ralph does not state what constitutes such "early stages." Ralph states directly "at very early stages of disease progression, when there are few or no circulating diseased cells present in the peripheral blood (Col. 5, lines 10-11; emphasis added)." Appellant argues that there is no clear teaching or suggestion that the method may be applied to very early stage breast cancer. KSR forecloses the argument that a specific teaching, suggestion or motivation is required to support a finding of obviousness (KSR 82, USPQ2d at 1396). Here a complete rational is given to support the obviousness of the claimed invention.

Appellant points to the passage at Col. 52 to support a position that Ralph makes clear that very early stage disease could encompass a metastasizing tumor. The portion quoted by Appellant, however refers to "early stages" of disease, not "very early stages." Ralph clearly states that they consider very early stages of disease progression to be when few or no circulating diseased cells are present. Appellant asserts that a person of ordinary skill would have expected that it was debris or cellular components of cancer cells which are responsible for the effects observed in Ralph, and that Ralph's method could only be extended to detecting cancers which reach metastatic potential or which are metastatic. There is no requirement set forth by Ralph that the subject cancer be a metastatic cancer, and as previously discussed there is direct suggestion to the contrary. Further, it would have been expected that leukocytes would have come in contact with even organ defined cancer since they were known to spend most of their time outside the circulatory system, patrolling through interstitial fluid and the lymphatic system.

Appellant states that if Ralph intended their teachings in column 5 to refer to "very early stage breast cancer" they would not have suggested that there could be few circulating disease

cells. However, this is not persuasive because Ralph also suggests that their method could be applied where there are no circulating disease cells in this same passage.

The examiner maintains that the same language was used in the present application and Ralph in referring to very early stage disease. Appellant points out that when Ralph refers to very early stage disease this is without reference to cancer or breast cancer (page 16). This is also true of the instant specification (specification page 11, third paragraph). Appellant points out that there is no reference to very early stage breast cancer anywhere in Ralph. There is also no specific reference to very early stage breast cancer in the instant specification. Appellant states that Ralph uses very early stages disease "in a very different way to the way it is used in the instant claims to reference a particular condition (breast cancer) which denotes a very specific stage, stage 0, of that cancer." Ralph et al. is specific that very early stage disease encompasses a situation where no disease cells are circulating. If appellant's disclosure of "very early stage disease" in one portion of the specification, and breast cancer as a subject disease in another portion of the specification is fairly construed to have put Appellant in possession of the claimed invention limited to methods concerned with stage 0 breast cancer, than so to is Ralph's very similar disclosure. Appellant refers again to the discussion of early stages of disease at column 52 of Ralph. This is distinct from the discussion of "very early stages of disease" where no cancer cells may be circulating, as previously discussed, because Ralph specifically teach that very early stages of disease includes disease states where no cells are circulating.

Appellant points out on page 17 that there are no technical examples in Ralph et al. which would make a person of ordinary skill think that Ralph intends for the method to be extended to the detection of cancers which have not yet reached metastatic potential. The teachings of Ralph

et al. which would have suggested this have been discussed previously in this office action. The reference is not limited to the exemplification, and must be considered for all it would have reasonably suggested to one having ordinary skill in the art.

Appellant continues to argue on page 17, final paragraph that even though Ralph et al. expressly state in Col. 10, line that their invention is applicable to organ defined cancers, Appellant believes that organ defined cancer could only have been interpreted to mean prostate cancer, referring to the discussion of Mackay his first declaration. Mackay points out that the examples are concerned with prostate cancer, and discusses the fact that early stage prostate cancer may have metastatic potential, while very early stage breast cancer does not. The brief reiterated this position on pages 18-19. The position taken in the declaration has been considered but it not persuasive, because it is an attempt to limit the teachings of Ralph to the examples provided while not considering the totality of the disclosure. This brief has previously discussed at length why the examiner believes that Ralph et al. was explicit in their position that their method could be applied to cancers in which there were no circulating cells, which are organ defined.

On page 19 the brief opines reasons as to why Ralph makes no reference to the detection of very early stage breast cancer. Ralph is express that their method could be applied to breast cancer (abstract) and organ defined disease (Col. 10) and disease where there are no circulating disease cells (Col. 5). Appellant's opinion as to why Ralph makes no reference to very early stage breast cancer is just that, an opinion, a speculation. Appellant reiterates their position that there was no expectation that the method would be successfully applied to early stage breast cancer. An absolute expectation of success is not a requirement for a showing of obviousness.

Appellant argues on page 20 of the brief that extension of Ralph's teachings to very early stage breast cancer is only possible with hindsight. However, this is not persuasive. Point in fact, Ralph et al. only specifically name two types of cancer in their disclosure: prostate cancer and breast cancer. Ralph is explicit that their disease is applicable to cancers where no circulating cells are present, referred to by Ralph as "very early stage disease." There were a finite number of cancer types expressly mentioned in Ralph to which one having ordinary skill could have applied this teaching. The examiner's conclusion is not the employment of hindsight, but instead the following of the express teachings of the reference to a logical end.

Appellant again reiterates the position that in view of the teachings of Ralph and the examples one having ordinary skill would have limited the invention to tumor cells with metastatic potential, which are not present in very early stage breast cancer (p. 19-22). These arguments have been addressed previously. Nonetheless, it is reiterated that Ralph et al. expressly suggest applying their method to organ defined cancers and very early stage disease where no circulating cells are present. Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments (MPEP 2123(II)).

On page 22 of the remarks Appellant reiterates the position that there would have been no reasonable expectation of success for detection of very early stage breast cancer. Again, it is reiterated, that in this case, there was a recognized problem in the art- as supported by Lukas- namely to identify markers for the detection of very early stage breast cancer, and the use of those markers to detect the condition. Ralph provide clear teaching of a method for screening for markers in blood samples, it is undisputed on this record that the molecular biology techniques

used by Ralph were routinely employed at the time the invention was made. The contribution provided by Ralph was to look to the blood for the detection of markers of disease at very early stages of disease, diseases which Ralph clearly discloses as including organ defined cancers and breast cancer. One of ordinary skill in the art could have employed the methods of finding the markers in patients having very early stage breast cancer, and, if the markers were present, would have had an excellent chance of success in identifying using the methodologies exemplified by Ralph or other routinely used methods for assay of expression levels of genes in the blood. As noted in the Supreme Court decision KSR, "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely that product [was] not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103." KSR 82 USPQ2d at 1397.

On page 23, Appellant repeats the argument that that one of ordinary skill in the art would not have been motivated to try the method disclosed by Ralph to detect cancers that have not reached metastatic potential or are non-metastatic. This argument is duplicative and has been previously addressed. It is not persuasive for the previously cited reasons.

On page 24, Appellant argues that Wadhwa does not cure the deficiencies of Ralph in view of Lucas. Since the rejection of Ralph in view of Lucas is maintained, so also is the further rejection in view of Wadhwa.

Appellant argues that the claim invention allows for the unexpected detection of non-metastatic or pre-metastatic very early stage breast cancer. Appellant points to the declaration of the inventor as evidence that the claimed methods discriminate between normal and very early

stage breast cancer with high accuracy. These results are not commensurate in scope with the claims because they do not show the result using only 10 probes, the minimum number required in most of the claims.

Further, and more importantly, however, based on the teachings of Ralph et al. these results are not unexpected, as Ralph et al. particularly suggests such a method, as discussed extensively in this Brief.

The rejection is maintained.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Juliet C. Switzer/,
Primary Examiner

Conferees:
/Dave Nguyen/
SPE, Art Unit 1634

/Kay Kim/
Primary Patent Examiner